I. REMARKS

Claims 1, 2, and 4 are pending in the present application, claims 3 and 5 having been previously canceled. All the pending claims were rejected, under 35 U.S.C. §103(a), over two different combinations of prior art references, described below. These were the only grounds of rejection of either of these two claims maintained, according to the Advisory Action, from the Final Office Action.

Given the above-cited remark from the Advisory Action, it appears the rejection, under 35 U.S.C. § 112, of claim 4 set forth in the Final Office Action, has been withdrawn in view of Applicant's amendments to that claim in response to that Action. (See response, filed 8/30/04).

Applicants respectfully traverse the rejections of claims 1, 2, and 4, in view of the following remarks:

A. Rejection of Claims 1 and 4, Under 35 U.S.C. §103(a), over Brown *et al.* (*Journal of Biological Chemistry,* Vo. 273, No. 39, pp. 25458-465, Sept. 25, 1998) in view of Harpold *et al* (WO 95/04822, 19 Feb. 1995)

Claims 1 and 4 were rejected, under 35 U.S.C. §103(a) as being unpatentable over Brown et al. in view of Harpold *et al.* Brown *et al.* is described in the Advisory Action as teaching "all of the limitations of claim 1", except for "the polypeptides recited in SEQ ID NOs: 13, 14, and 15. (Advisory Action, p. 6). Harpold *et* al is cited as teaching a sequence "comprising the polypeptide sequences of SEQ ID NOS: 13, 14, and 15." (citing SEQ ID NO: 11 of Harpold *et al.* (*Id.*) The same references is also cited for providing motivation to select sequences from the larger sequence and using them in assays such as those taught by Brown *et al.* (*Id.*) The Advisory Action also states that Harpold *et al.* establishes a reasonable expectation of success of using fragments of the full length sequence in the ligand screening method of Brown *et al* by teaching that "any fragment or modified peptide of the larger sequences can be utilized in various assay systems as long as the function of the peptide or fragment thereof is maintained." (Advisory Action, p. 7).

Applicants respectfully submit that the broad statement from Harpold *et al.* regarding the production of polypeptides from proteins, and maintaining a given activity, does not provide an expectation of success in the production of the particular type of polypeptide, a soluble polypeptide, used in the screening method of the present invention. Harpold *et al* discloses native sequence of human $\alpha_2\delta$, and refers to its potential use in ligand binding assays. Harpold *et al.* additionally refers to peptides of the human $\alpha_2\delta$ subunit which have the same function and activity as the full length sequence. Harpold *et al.* is silent on the issue of how to provide a soluble $\alpha_2\delta$ polypeptide subunit, and fails to suggest that provision of such a soluble polypeptide is possible or desirable.

The polypeptides used in the present method (SEQ ID NOs: 13, 14, and 15) are new, soluble, forms of human $\alpha_2\delta$-1, characterized by a C-terminus truncation, polypeptides with an active gabapentin binding site. (See current specification, p. 5, lines 7-10). Applicants submit that Brown *et al.* viewed in combination Harpold *et al.* neither teach nor suggest the selection of any such polypeptide for use in a ligand screening method such as the method of claim 1. This fact is particularly clear, in view of the evidence found in Brown *et al.*, of the unpredictability of selecting soluble calcium channel $\alpha_2\delta$ subunit polypeptides with sufficient activity to make them useful in screening methods of the type claimed herein.

Brown *et al.* discloses a method of screening $\alpha_2\delta$ ligands, using 14 polypeptides obtained by truncating the C-terminus of proteins from cloned porcine $\alpha_2\delta$. The polypeptides were specifically obtained by truncating the C-terminus from various residues between 111 and 1061 to the end of the protein. One of the truncated proteins obtained, designated mutant L, lacked most of the D transmembrane domain and, unlike the other polypeptides assayed, displayed partial soubility and good ligand binding ability. That was the only polypeptide identified by Brown *et al.* as being soluble.

Brown *et al.*, specifically, postulates that the D transmembrane domain (Fig 1 Brown *et al.*: Domain IV 1035-1060) is responsible for anchoring the protein to the membrane, and that by merely removing this domain the skilled person will produce a soluble protein. However, this was clearly not the case, as is apparent from the experimental results disclosed in the same reference. In only one of the 14 $\alpha_2\delta$

truncations illustrated therein (mutant L), where the D transmembrane domain was removed, the resulting polypeptides were not soluble. Brown *et al.* notes:

> "All of the $\alpha_2\delta$ deletion mutants whose expression could be confirmed by Western blotting were detected in particulate fractions. However, large scale expression of mutant L (deletion 1040 - 1067) yielded a soluble as well as a membrane associated form", Brown *et al.*, page 25464, final pargraph.

Brown *et al.* concludes by commenting on the inability of the transmembrane model to explain the properties of the subunits of $\alpha_2\delta$ disclosed therein.

In view of the above, Applicants respectfully submit that Brown *et al.* viewed in combination with Harpold *et al.* demonstrate that it would have been unpredictable for one of ordinary skill in the art of the present invention to select any one of the three specific polypeptides of SEQ ID NO's 13, 14, or 15 for use in the method of screening of the present invention. Given this unpredictability, Applicants respectfully submit that one of ordinary skill in the art would not have had the requisite motivation to modify the teachings of either or both references to select any of the three polypeptides of claim 1 for use in the present claimed method.

For reasons set forth above, therefore, Applicants respectfully traverse the rejection of claims 1 and 4, under 35 U.S.C. §103(a), over Brown *et al.* in view of Harpold *et al,* and respectfully request that this rejection be withdrawn.

C. Rejection of Claim 2, under 35 U.S.C. §103(a), over Brown *et al.* in view of Harpold *et al.* and further in view of Holland *et al.* (*Analytical Biochemistry,* November 1994)

Claim 2 was rejected, under 35 U.S.C. §103(a), over Brown *et al.* in view of Harpold *et al.* for reasons applied to claims 1 and 4, above, further in view of Holland *et al.* Holland *et al.* is cited in the Office Action as teaching a "screening method of screening ligands using a flashplate assay, wherein the contacting and binding is in the wells of a flashplate." (Office Action, p. 5).

Claim 2 relates to a specific format of the method of screening ligands, of claim 1. Holland *et al.* fails to teach or suggest the use of any of the three polypeptides used in the method of claim 1, or to provide a reasonable expectation that any of the three

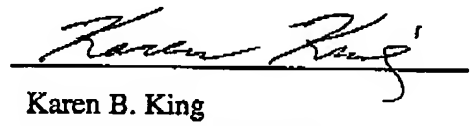
polypeptides would work in the method of claim 1 when viewed with Brown *et al.* and Harpold *et al.* See above for a specific discussion of why the subject matter of claim 1 is non-obvious over Brown *et al.* in view of Holland *et al.*

For reasons set forth above, Applicants respectfully traverse the rejection of claim 2, under 35 U.S.C. §103(a), over Brown *et al.* in view of Harpold *et al.*, and further in view of Holland *et al.*

II. SUMMARY

Applicants respectfully submit that all of the present pending claims (i.e., claims 1, 2, and 4) are in condition for allowance, for reasons set forth above. Issuance of all the claims is, therefore, requested. The Examiner is invited to contact the undersigned at the telephone number given below, should she wish to discuss the present amendment and suggest additional changes to the claims in order to further prosecution of the application.

Dated: 1/28/05



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